

REMARKS

Claims 7, 8, 14, 16, 19 and 20 are currently withdrawn from consideration. Claims 9, 10, and 17-20 have been canceled herein. Claims 1-6, 11-13 and 15 are currently under examination. In light of the claims cancelations noted above and the remarks below, Applicants respectfully request reconsideration of the pending claims.

Claim Objections

The Office has rejected claims 9, 10 and 17-20 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The office has requested Applicants to cancel the claims, amend the claims to put them into proper dependent form, or to re-write the claims in independent form. In response, Applicants have cancelled claims 9, 10 and 17-20. Accordingly, Applicants request that the Office withdraw these claim objections.

Claim Rejections 35 U.S.C. 112

The Office has rejected claims 9, 10, 17 and 18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Office objects to the term "a derivative" in line 1 of claims 9 and 17. The Office asserts that there is insufficient antecedent basis for this limitation in the claim.

In response and without agreeing with the Office's assertion, Applicants have herein cancelled claims 9, 10, 17 and 18. Accordingly, Applicants respectfully request the Office to withdraw these rejections.

Claims Rejections 35 U.S.C. 102

The Office has rejected claims 9, 10, 17 and 18 under 35 U.S.C. 102(b) as being anticipated by Korant (WO 00/21565). Specifically, the Office asserts that all the limitations of those claims are taught by Korant. The Office has similarly rejected claims 9, 10, 17 and 18 under 35 U.S.C. 102(e) as being anticipated by Stuyver (US 2005/0049220). Specifically, the Office asserts that all of the limitations of those claims are taught by Stuyver. Applicants notes that claims 9, 10, 17 and 18 have been cancelled herein. Accordingly, Applicants

respectfully request that the Office withdraw the anticipation rejections contained in this Office Action.

Claims Rejections 35 U.S.C. 103

The Office has rejected claims 1-6, 9-13, 15, 17 and 18 under 35 USC 103(a) as being unpatentable over Korant (WO 00/21565), in view of Gunnarsdottir et al. (J. Pharmal Exp. Therapeutics 301 (2002): 77-86). The Office alleges that Korant teaches a method of treating hepatitis C infection comprising administering to the patient a cytotoxic agent, such as 6-mercaptopurine (6-MP). In addition, the Office alleges that Gunnarsdottir et al. disclose that AVTP is a known pro-drug of 6-mercaptopurine with less bone marrow toxicity. (The Office actually made this assertion regarding "AVTG," which is not a recited compound. Applicants presume that this was a clerical error.) Thus, one skilled in the art would be motivated to combine the teachings of the reference to administer AVTP to patients having hepatitis C.

Applicants note that claims 9, 10, 17 and 18 have been canceled. Because there is no reasonable expectation of success for a skilled artisan at the time of the invention to combine the cited references to practice the claimed invention, and because the references as a whole teach away from the claimed invention, the obviousness rejection is improper.

In obviousness rejections, the references must be combinable with a reasonable expectation of success. MPEP 2143.02. In this case, because the references themselves teach that the compounds in question are cytotoxic agents useful in killing whole cells (HIV infected cells or tumor cells) rather than useful to specifically inhibit viral replication, the references do not provide a skilled artisan with sufficient guidance to give the skilled artisan a reasonable expectation of success in combining teachings of the references to produce the claimed invention.

The Office is directed to the as-filed specification which outlines the advantages of the present invention over the previous art. AVTP is a nucleoside analog that specifically inhibits + sense RNA virus replication, while possessing reduced systemic toxicity as compared to previously known anti-viral agents (see e.g. paragraphs [14], [39] and Examples). Thus, AVTP was found to be a more useful anti-viral than previous agents as higher viricidal doses can be achieved without the numerous side-effects observed with the previous agents. In fact, viral suppression using the presently claimed method works even in the complete absence of cellular toxicity (paragraph [46]). In addition, as compared to metabolites such as 6-MP, AVTP specifically targets glutathione rich tissue such as the liver and kidney. For there to be

sufficient guidance for reasonable expectation of success in combining any cited references to practice the claimed method, then, there must be an indication in the references that AVTP successfully targets RNA virus replication while not reducing cell survival, particularly in glutathione-rich tissues.

The cited references on the other hand, indicate that the compounds AVTP and 6-mercaptopurine are highly toxic and thus could not be successfully used in the claimed invention. Korant teaches that HIV infection can be treated by using a combination of a cytotoxic agent and an anti-viral agent (abstract, page 4). By combining the two separate agents, high load cells containing the virus are destroyed and at the same time the virus is prevented from spreading because of the included anti-viral agent. The two agents supposedly work together in synergy to effectively treat illnesses such as HIV and hepatitis C (page 13).

Korant teaches that the cytotoxic agent is one of a large number of possible compounds, including 6-mercaptopurine (page 6, line 17). Significantly for the skilled artisan seeking guidance, 6-mercaptopurine is not taught as a possible anti-viral agent (page 7, lines 24-29). Korant clearly teaches the skilled artisan that 6-mercaptopurine is used to kill cells, not to target viral reproduction. On the other hand, Korant discloses a number of anti-viral agents including, for example, lamivudine and famcyclovir. 6-mercaptopurine is not among the anti-viral agents that are taught in Korant. Thus, the skilled artisan would not expect success using 6-mercaptopurine (or its prodrugs) as an anti-viral agent alone as something that would inhibit viral replication while limiting cytotoxicity, as it does in the present invention. In fact, by designating 6-mercaptopurine as a cytotoxic agent and not an antiviral agent, Korant teaches away from using a 6-mercaptopurine based method for this purpose. Given that the present invention is designed to inhibit viral replication along with reduced cytotoxicity, the skilled artisan would be discouraged from using that particular compound or any of its pro-drugs, and would have no reasonable expectation of success in using these compounds for this purpose.

Nothing in Gunnarsdottir et al. cures this deficiency by teaching or suggesting the use of AVTP as an anti-viral agent. In fact, Gunnarsdottir et al. teach that although AVTP has decreased bone marrow toxicity as compared to 6-MP, it is actually more cytotoxic to glutathione-rich tissues than 6-MP (see e.g. Table 2, page 83 and discussion on page 84, col. 2 and 85). In the context of Gunnarsdottir et al. (use in chemotherapy against tumors), reduced bone marrow toxicity and increased cytotoxicity against glutathione-rich tissues (such as tumor cells) are both advantageous. However, to the skilled artisan targeting viral

replication in glutathione-rich tissues while minimizing cytotoxicity in the target tissues (as in the present method), Gunnarasdottir et al. (1) provide no guidance whatsoever regarding anti-viral activity, and (2) teach away from the use of AVTP as an agent having reduced cytotoxicity.

Together, then, the two references do not provide the skilled artisan with sufficient guidance to produce the claimed method with any degree of predictable success and in fact actively teach away from the claimed method. Thus, the rejection of the claims is improper and Applicants respectfully request reconsideration and a withdrawal of the rejections.

The Office has rejected claims 1-6, 11-13 and 15 under 35 USC 103(a) as being unpatentable over Stuyver (US 2005/0049220), in view of Gunnarasdottir et al. (J. Pharmal Exp. Therapeutics). The Office alleges that Stuyver teaches a method of treatment of Hepatitis C comprising administering a patient a compound 6-mercaptopurine and that Gunnarasdottir et al. disclose that AVTP is a known pro-drug of 6-mercaptopurine with less bone marrow toxicity. Thus the skilled artisan would be motivated to combine the teachings of Gunnarasdottir et al. and Stuyver to produce the method of the claimed invention. Because the cited documents do not give sufficient guidance the skilled artisan would not have a reasonable expectation of success and because the cited documents teach away from the claimed invention, the obviousness rejections are not proper.

As pointed out previously, one of the features of the presently claimed invention is that the AVTP has surprisingly low cytotoxicity relative to other known anti-viral agents. Thus, the use of AVTP allows for higher dosages of anti-viral than have previously been used. Stuyver discloses using an ant-metabolite as an anti-hepatitis C agent that cannot be administered on a daily or chronic basis because of its cytotoxicity (see e.g. paragraph [0061]). In fact, the heart of Stuyver is a dosing regimen that allows for the dosing of the anti-viral agent without excessive cell death caused by daily dosage. Thus, the disclosed treatments taught by Stuyver inherently have high cytotoxicity, and thus the skilled would not expect success in using treatments in the presently claimed method.

In Stuyver, 6-mercaptopurine is mentioned in a list of a large number of purine analogs and related inhibitors that could be used in the invention (paragraph [0100]). Stuyver contains no guidance as to which, if any, of the compounds would have lower cytotoxicity (and, as discussed above, Stuyver implies that all the disclosed compounds have high cytotoxicity). As an illustration of this lack of guidance, in the same paragraph that suggests using 6-mercaptopurine, Stuyver also suggest using 6-thioguanine, which the present inventors have

found is not appropriate for use in the present method. Thus, Stuyver gives no guidance indicating which of the listed cytotoxic agents could be effective anti-virals in a situation where low toxicity is desired.

Nothing in Gunnarsdottir et al. cures this deficiency by teaching or suggesting the use of AVTP as a less toxic anti-viral agent. In fact, Gunnarsdottir et al. teach that although AVTP has decreased bone marrow toxicity as compared to 6-MP, it is actually more cytotoxic to glutathione-rich tissues than 6-MP (see e.g. Table 2, page 83 and discussion on page 84, col. 2 and 85). In the context of Gunnarsdottir et al. (use in chemotherapy against tumors), reduced bone marrow toxicity and increased cytotoxicity against glutathione-rich tissues (such as tumor cells) are both advantageous. However, to the skilled artisan targeting viral replication in glutathione-rich tissues while minimizing cytotoxicity in the target tissues (as in the present method), Gunnarsdottir et al. (1) provide no guidance whatsoever regarding anti-viral activity, and (2) teach away from the use of AVTP as an agent having reduced cytotoxicity.

Together, then, the two references do not provide the skilled artisan with sufficient guidance to produce the claimed method with any degree of predictable success and in fact actively teach away from the claimed method. Thus, the rejection of the claims is improper and Applicants respectfully request reconsideration and a withdrawal of the rejections.

Conclusion

A petition and fee for a Three-Month Extension of Time is enclosed. If any additional fees are needed, please charge Deposit Account 17-0055. The Commissioner is hereby authorized to deduct any fees arising as a result of this or any other communication in this matter from Deposit Account 17-0055.

Respectfully submitted,

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